CLINICAL DATA FOR CONFORMITY ASSESSMENT AND REGULATORY APPROVAL

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CLINICAL DATA

What are Clinical Data?

Generated from the application and use of a medical device

Performance

- Actual device, equivalent device (narrow equivalence)

Safety

- Actual device, equivalent device (wide equivalence)

Clinical benefit (benefit-risk-ratio)

- Actual device, equivalent device
- Clinical procedure

CLINICAL DATA

Sources of Clinical Data

Clinical investigations with the actual device

Clinical investigations with equivalent devices

Other clinical studies with the actual device or equivalent devices

Scientific literature (peer reviewed) – performance, benefit, safety

- Studies/investigations with the actual device, equivalent devices

Other publications – safety (complications, side effects)

- Also, case reports, congress papers, etc.

Relevant clinical data from surveillance of the product after market approval

- PMS, PMCF

MEDDEV 2.7/1 REV.4 (MDR)

Clinical Investigations

If gaps are present that cannot be addressed by other means, clinical investigations should be planned and carried out.

Implants and high-risk devices, those based on technologies where there is little or no experience, and those that extend the intended purpose of an existing technology (i.e. a new clinical use) are most likely to require clinical investigation data.

Clinical investigations may also be required for other devices, including for devices in class I and class IIa, and for class IIb devices that are not implantable.

NB: It can be difficult/impossible to find or generate clinical data for tools (e.g., scalpels, anesthesia machines), long-standing technologies (e.g., mechanical ventilators), or medical-technical accessories (e.g., ventilation hoses).

NB: Gaps become wider from the increasing requirements for equivalence between devices.

CLINICAL INVESTIGATIONS

Evidence of performance and safety in a prospective clinical trials

- Not (yet) approved/certified medical devices
- Expansion of the intended use

Approval from the competent authority (BfArM, FDA, …)

- Studies within the intended use ➔ §23b MPG

Clinical investigation

- Only after exhaustive preclinical testing (e.g., biomechanics, animal studies)
- Full risk management, etc.

Strict requirements for study design and statistical planning

PMCF STUDIES

Clinical data after market approval of the device

- Safety
- Performance
- Unknown side effects, complications, contraindications
- Continuous assessment of the benefit-risk-ratio

Potential PMCF studies:

- Registers, retrospective analysis of prospectively collected clinical data
- Observational studies
- User surveys (including proactive PMS)
- Long-term follow-up of pivotal trials
- Prospective comparative trials in case of open questions in the CER (e.g., established class III products)

OFF-LABEL USE

Clinical application outside the intended use

- Different indication, application
- Different patient population
- Individual case ➔ Compassionate trial
- Systematic off-label use ➔ new intended use (or too narrow initial intended use)

Studies with off-label use

- Investigator initiated trials (IITs) outside the intended use
- Only studies sponsored by the manufacturer and planned for this purpose can be used for expanding the intended use

IIT

Investigator Initiated Trial

A study initiated and managed by non-industry researchers, like individual investigators, institutions, collaborative study groups or cooperative groups.

Pros for the manufacturer:

- Less cost, less effort
- Only limited internal competence needed
- Less formal hurdles/efforts

Cons for the manufacturer:

- Individual interests of the PIs
- Clinical data “owned” by PIs
- Incomplete monitoring
- Sometimes non-optimal study quality
- No direct control by the manufacturer

STUDY SPONSOR

What/who is a study sponsor?

Def (MDR): ‘sponsor’ means any individual, company, institution or organization which takes responsibility for the initiation, for the management and setting up of the financing of the clinical investigation.

Manufacturer as sponsor:

- Required in clinical investigations
  (for conformity assessment / regulatory approval)
- Required in studies for expanding the intended use

Sponsorship is not required for studies within the intended use
(e.g., PMCF studies)

STUDY SPONSOR

Why does it make sense to be a study sponsor?

Advantages

- Full control over the study
- Complete access to data/results
- Full control over publication of the data
- Optimal quality

Disadvantages

- Higher cost
- Company internal competence helpful/necessary
- Less scientific “appeal” for the PIs

CLINICAL STUDIES

qtec

Prospective vs. Retrospective Studies

Prospective studies

+ Typically better quality (higher level of evidence)
+ Better control of confounders
+ Planning according to a specific research question feasible
+ Good data quality
- Long time until study results are available
- Typically limited case numbers
- Typically narrow populations and target criteria
- Potential hurdles with IRB, approval from competent authority

Retrospective studies

+ Short time to results
+ Large case number feasible
+ Low hurdles with IRB, no approval from competent authority needed
- Study design quite restricted
- Difficult control of confounders
- Often incomplete data sets
- Not appropriate for new products (except for new regions)

CLINICAL STUDIES

General recommendations

Study design according to desired intended use

- Adequate study population
- Adequate study criteria

Sponsor initiated studies!

GCP, ISO 14155 (also for study acc. to §23b MPG!)

Adequate study monitoring (e.g., CRO)

All potentially relevant regulatory pathways should be considered from the beginning (CE, FDA, …)

Maintain full control over the study and the study data!

The most expensive studies are those without helpful/useful results!

ALTERNATIVES

Alternatives to clinical data

MDR and MEDDEV 2.7/1 Rev 4 refer to clinical data only!

Preclinical data are not explicitly mentioned as substitute for clinical data

Issues of clinical investigations (esp. for low/no-risk devices/procedures):

- Procedures cannot be tested across the entire application range without endangering patients
- Vulnerable populations are difficult to recruit
- Reference methods can be more invasive than the tested method/device

Especially diagnostic devices and devices that are tools are affected.

Alternatives/supplements to clinical studies:

- Compliance with standards
- Animal studies (mostly large animal models)

EXAMPLES

Implant Class III – New Product

Clearly defined indication and therapeutic benefit

First-in-men study

Clinical investigation (pivotal trial)

- Requirements under MDR (probably) stricter, but nothing entirely new
- Coordination with FDA activities should always be considered

Clinical investigation often answers questions about the clinical benefit

Use of data from equivalent devices very limited

- Equivalence can effectively be only established for products from the same manufacturer

Comprehensive PMCF plan

- Long-term follow-up of the clinical investigation
- Register studies

EXAMPLES

Implant Class III – Existing Product

Clearly defined indication and therapeutic benefit

Previous conformity assessment often with limited or no data from clinical investigations (pivotal trials)

Clinical data from equivalent products

- In many cases equivalence cannot be established under MDR

PMCF-Studies

- Implant registers, product-specific registers
- Data from other regions (e.g., USA)
- Data for other approval processes

Always detailed post-market surveillance

Additionally proactive post-market surveillance

CONCLUSIONS

Clinical Data for Conformity Assessment

Clinical data required for all medical devices

- Including devices of classes IIb, IIa, and I

Clinical data previously considered adequate may not be sufficient under MDR anymore

Alternative data sources (standards, animal trials) not explicitly considered under MDR/MEDDEV

Not using clinical data requires detailed argumentation

PMCF, proactive PMS

Clinical investigations may be required

Don’t be afraid of sponsor-initiated studies (ISO 14155, GCP)

- May be required anyhow!

Coordination with FDA activities!